DATA EVALUATION RECORD

PICOXYSTROBIN (ZA1963)

Study Type: OPPTS 870.3700a [§83-3a]; Developmental Toxicity Study in Rats

Work Assignment No. 7-01-256 (MRID 48073738)

Prepared for
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Template version 02/06

DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Toxicity Study in Rats (gavage); 870.3700a [§83-3a]; OECD 414.

PC CODE: 129200 **DP BARCODE:** D378236
TXR#: 0056696 **SUBMISSION #:** S873059

TEST MATERIAL (PURITY): Picoxystrobin (99% a.i.)

SYNONYMS: ZA1963; Methyl (α*E*)-α-(methoxymethylene)-2-[[[6-(trifluoromethyl)-2-pyridinyl]oxy] methyl]benzeneacetate

CITATION: Moxon, M.E. (1998) ZA1963: Developmental toxicity study in the rat. Central Toxicology Laboratory, Alderley Park, Cheshire, UK. Laboratory Project Study ID: RR0702, April 2, 1998. MRID 48073738. Unpublished.

SPONSOR: E.I. du Pont de Nemours and Company, Wilmington, DE

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 48073738), ZA1963 (Picoxystrobin; 99%; Batch No. P9) in corn oil was administered via daily oral gavage in a dose volume of 10 mL/kg to 24 time-mated Alpk:AP$_f$SD (Wistar-derived) rats/dose group at doses of 0, 10, 30, or 100 mg/kg/day from gestation days (GD) 7-16 inclusive. On GD 22, all dams were euthanized; each dam's uterus was removed via cesarean section and its contents examined. Fetuses were examined for external, visceral, and skeletal malformations and variations.

No treatment-related effects on mortality, gross pathology, or cesarean section data were observed in the dams at any dose.

At 100 mg/kg/day, clinical signs including signs of diarrhea, diarrhea, and urine staining were observed in 6-9 dams during the dosing period. Also in this group, body weight gains (calculated by reviewers) were decreased by 22% compared to controls during the dosing period (GD 7-16) and 7% for the overall (GD 1-22) study; body weights were decreased ($p<0.01$) by 3-4% at all intervals during dosing and on GD 19; and food consumption values were decreased ($p<0.01$) by 13-35% compared to controls throughout the dosing period.

The maternal LOAEL is 100 mg/kg/day based on decreased body weight gain, food consumption, and increased incidence of clinical signs (diarrhea and urine staining). The maternal NOAEL is 30 mg/kg/day.

There were no abortions, premature deliveries, complete litter resorptions, or dead fetuses and no effects of treatment on the numbers of litters, live fetuses, early resorptions, or late resorptions. Similarly, sex ratio and post-implantation losses of the treated groups were comparable to controls.
There were no effects of treatment on growth or development of the fetuses. Fetal weights of the treated groups were comparable to controls, and there were no treatment-related effects on ossification of the skeleton.

There were no adverse treatment-related external or visceralvariations or malformations. At 100 mg/kg/day, an increased incidence of misaligned 5th sternebrae was observed and regarded as an adverse effect of treatment.

The developmental LOAEL is 100 mg/kg/day based on misaligned 5th sternebrae. The developmental NOAEL is 30 mg/kg/day.

This study is classified **acceptable/guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700a; OECD 414) in rats.

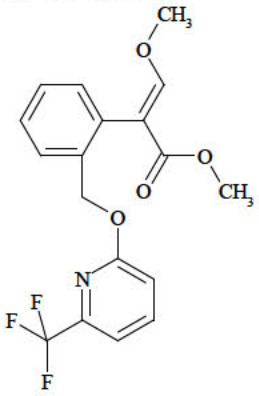
COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: ZA1963

Description: White solid
Lot #: P9
Purity: 99%
Compound stability: The test material was shown to be stable in the vehicle for up to 34 days at room temperature
CAS #: 117428-22-5
Structure:



2. Vehicle: Corn oil

3. Test animals

Species: Rat
Strain: Alpk:AP$_f$SD (Wistar-derived)
Age/ Group mean weight at GD 1: Approximately 10-12 weeks; 214-307 g
Source: Rodent Breeding Unit (Alderley Park, UK)
Housing: Individually in cages on racks.
Diet: CT1 Diet (supplier not reported), *ad libitum*
Water: Tap water, *ad libitum*
Environmental conditions:
Temperature: 21±2°C
Humidity: 40-70%
Air changes: 25-30/hr
Photoperiod: 12 hrs light/12 hrs dark
Acclimation period: None. Successfully mated females were delivered to Central; Toxicology Laboratory on GD1.

B. PROCEDURES AND STUDY DESIGN

1. In-life dates: Start: August 1, 1995 End: September 1, 1995

2. Mating: Sexually mature, nulliparous females were mated with males of the same strain at the supplier's facility. The following morning, females were examined for positive evidence of mating, as confirmed by the presence of spermatozoa in a vaginal smear. The day on which the presence of spermatozoa in a vaginal smear was detected was designated gestation day (GD) 1. The animals were delivered to the performing laboratory on GD 1.

3. **Animal assignment:** Time-mated female rats were randomly assigned to the treatment groups shown in Table 1.

TABLE 1. Animal Assignment [a]				
Dose (mg/kg/day)	0	10	30	100
No. females	24	24	24	24

a Data were obtained from page 16 of the study report.

4. **Dose selection rationale:** It was stated that the doses for the current study were based on the results of a dose range-finding study in pregnant rats performed in the laboratory. However, no further details were provided.

5. **Dose preparation, administration, and analysis:** For each concentration, the appropriate amount of the test material (adjusted for purity) was suspended in corn oil. Each preparation was subdivided into aliquots and stored at room temperature.. The dose suspensions were administered to the animals daily from GD 7-16 via oral gavage in a dose volume of 10 mL/kg body weight. Dose volumes were adjusted daily based on individual body weights. Homogeneity of the test substance in the vehicle was confirmed in the high-dose (10 mg/mL concentration) only. Concentration analyses were performed on samples of each dose level prior to initiation of dosing. Stability analyses were performed on the 1 and 10 mg/mL concentrations following room temperature storage for 34 days.

Results

Homogeneity (% RSD): 0.0 to 1.0%

Concentration (mean % nominal): 97.0-99.3%

Stability (% of initial): 101% for both the low and high concentrations

The analytical data indicated that the mixing procedure was adequate and the variation between the nominal and actual dosage to the animals was acceptable

C. OBSERVATIONS

1. **Maternal observations and evaluations:** Detailed clinical observations were performed daily and, when appropriate, at the same time that body weights were recorded. Cage-side observations were performed as soon as possible after dosing, and daily towards the end of the day. Individual body weights were recorded on GDs 1 (arrival), 4, 7-16 (inclusive, immediately prior to dosing), 19, and 22. Individual food consumption was recorded for each rat for GD 1-4, 4-7, 7-10, 10-13, 13-16, 16-19, and 19-22, and mean daily food consumption (g/rat/day) was calculated from these data for these intervals. On GD 22, all surviving dams were euthanized by halothane inhalation and subjected to a gross necropsy. The gravid uteri were weighed. The uterine contents were examined, and the number and position of implantations were subdivided into live fetuses and early or late

intra-uterine deaths, and the numbers of corpora lutea were recorded. In order to verify pregnancy status, the uteri from females lacking visible implantations were stained with ammonium polysulfide and examined for evidence of early resorptions.

2. **Fetal evaluations:** All fetuses were individually weighed and an external examination was made together with an examination of the oral cavity. All fetuses were then examined internally for visceral abnormalities, sexed, eviscerated, and fixed in 70% industrial methylated spirits. After approximately 24 hours the head of each fetus was cut along the fronto-parietal suture line and the brain was examined for macroscopic abnormalities. The carcasses were returned to 70% industrial methylated spirits for subsequent processing and staining with Alizarin Red-S. The remaining stained skeletons were examined for abnormalities and the degree of ossification was assessed using the scoring criteria provided in Appendix D on page 61 of the study report (provided as an Attachment to this DER).

D. DATA ANALYSIS

1. **Statistical analyses:** Statistical differences between control and treated groups were expressed at the 1% or 5% level. Animals which were non-pregnant or died intercurrently were excluded from analysis.

PARAMETER	STATISTICAL ANALYSES [a]
Body weight	ANCOVA based on initial (Day 7) body weight
Food consumption Numbers of implantations and live fetuses/female Gravid uterus weight Litter weight Mean fetal weights/litter Mean *manus* and *pes* scores/litter	ANOVA
Maternal performance data Proportion of fetuses with each individual *manus* and *pes* score Proportion of fetuses with each defect Proportion of litters with each defect	Fisher's Exact Test

a All analyses were carried out in SAS (1989). For Fisher's Exact Tests the proportion in each treated group was compared to the control group proportion. Analysis of variance and covariance allowed for the replicate structure of the study design. Least-squares means for each group were calculated using the LSMEAN option in SAS PROC GLM. Unbiased estimates of differences from control were provided by the difference between each treatment group least-squares mean and the control group least-squares mean. Differences from control were tested statistically by comparing each treatment group least-squares mean with the control group least squares mean using a two-sided Student's t-test, based on the error mean square in the analysis.

It was not stated whether the assumption of normal distribution of the data was tested prior to proceeding with parametric analyses. Otherwise, the statistical analyses were considered appropriate.

2. **Indices:** The following indices were reported:

Pre-implantation loss (%) = (# corpora lutea – # implantations)/ # corpora lutea x 100
Post-implantation loss (%) = (# implantations - # live fetuses)/ # implantations x 100

3. **Historical control data:** Not provided.

II. RESULTS

A. MATERNAL TOXICITY

1. **Mortality and clinical signs of toxicity:** One 30 mg/kg/day dam was killed on GD 10 following an accidental injury. All remaining animals survived to scheduled sacrifice. Treatment-related clinical signs were limited to signs of diarrheaand urine staining observed in 6-9 animals at 100 mg/kg/day during the dosing period. Evidence of post-dosing salivation was observed in 2 and 3 animals at 30 and 100 mg/kg/day, respectively.

2. **Body weight:** At 100 mg/kg/day, body weight gains (calculated by reviewers) were decreased by 22% compared to controls during the dosing period (GD 7-16) and 7% for the overall (GD 1-22) study (Table 2). Also at this dose, body weights were decreased ($p \leq 0.01$) by 3-4% at all intervals during dosing and on GD 19.

TABLE 2. Selected mean (±SD) maternal body weights and body weight gains (g). [a]

Gestation day (GD)	Dose (mg/kg/day)			
	0 (n=24)	10 (n=24)	30 (n=22)	100 (n=24)
Body weights				
GD 1	255.0±25.0	256.4±24.8	249.3±17.9	255.0±18.8
GD 7	287.5±23.2	290.8±26.4	282.3±17.5	286.8±20.3
GD 8 Mean	289.2±22.9	294.0±24.6	284.6±17.0	279.0±18.0
GD 8 Adjusted mean[b]	288.7	290.4	289.2	279.2** (↓3)
GD 16 Mean	344.0±22.8	349.3±24.0	338.8±17.2	331.2±20.0
GD 16 Adjusted mean[b]	343.5	345.7	342.6	331.3** (↓4)
GD 19 Mean	381.8±24.4	390.7±27.3	378.4±16.6	365.2±21.3
GD 19 Adjusted mean[b]	381.3	387.0	382.1	365.3** (↓4)
GD 22 Mean	396.9±26.5	396.5±33.0	402.8±22.5	387.4±22.6
GD 22 Adjusted mean[b]	396.4	392.7	407.4* (↑3)	387.6
Body weight gains [c]				
Pre-treatment GD 1-7	32.5	34.4	33.0	31.8
Treatment GD 7-16	56.5	58.5	56.5	44.4 (↓22)
Overall gain GD 1-22	141.9	140.1	153.5	132.4 (↓7)
Mean Gravid uterus (g)	86.1±14.3	96.3±12.0**	89.1±15.4	95.6±11.3*
Adjusted body weight gain (g)[c]	56	44	64	37

a Data were obtained from Table 6 on pages 34 and 35 of the study report. Percent difference from controls (calculated by reviewers) is presented parenthetically.
b Analyzed by analysis of covariance using GD 7 body weight as a covariate.
c Calculated by reviewers from data within this table.

* Significantly different from controls at p≤0.05
** Significantly different from controls at p≤0.01

3. Food consumption: At 100 mg/kg/day, maternal food consumption values were decreased (p≤0.01) by 13-35% compared to controls throughout the dosing period (Table 3).

TABLE 3. Mean (±SD) maternal food consumption (g/rat/day). [a]

Gestation day (GD)	Dose (mg/kg/day)			
	0 (n=24)	10 (n=24)	30 (n=22)	100 (n=24)
1-4	22.6±2.6	23.0±3.1	22.7±3.1	22.2±2.2
4-7	25.0±2.6	26.7±3.1	24.9±2.1	25.2±2.4
7-10	22.4±3.7	23.7±3.4	21.3±3.3	14.6±3.7** (↓35)
10-13	25.4±2.3	26.3±3.1	24.9±3.7	20.4±3.1** (↓20)
13-16	26.0±2.3	27.0±2.3	26.1±2.4	22.7±3.7** (↓13)
16-19	31.0±2.7	32.5±3.0	32.9±2.8	31.8±3.9
19-22	24.3±7.4	21.8±6.6	27.9±5.3	27.2±5.9

a Data were obtained from Table 7 on page 36 of the study report. Percent difference from controls (calculated by reviewers) is presented parenthetically.
** Significantly different from controls at p≤0.01

4. Gross pathology: No treatment-related gross lesions were observed at any dose.

5. Cesarean section data: Summary data from the cesarean sections are presented in Table 4. There were no abortions, premature deliveries, complete litter resorptions, or dead fetuses and no effects of treatment on the numbers of litters, live fetuses, early resorptions, or late resorptions. Similarly, fetal weights, sex ratio, and post-implantation losses of the treated groups were comparable to controls.

TABLE 4. Cesarean section observations [a]				
Observation	**Dose (mg/kg/day)**			
	0	**10**	**30**	**100**
# Animals assigned (mated)	24	24	24	24
# Animals pregnant	24	24	23	24
Pregnancy rate (%)	100	100	95.8	100
# Non-pregnant	0	0	1	0
Maternal wastage				
No. died	0	0	1	0
No. died pregnant	0	0	1	0
No. died non-pregnant	0	0	0	0
No. aborted	0	0	0	0
No. premature delivery	0	0	0	0
Corpora lutea **Corpora lutea/dam**	382 15.9±1.7	390 16.3±1.8	343 15.6±1.8	386 16.1±1.2
Total no. implantations **Implantations/dam**	327 13.6±2.6	365 15.3±2.0* (↑13)	303 13.8±2.6	350 14.6±1.9
Total no. litters	24	24	22	24
Total no. live fetuses **Live fetuses/dam**	293 12.9±2.7	342 14.9±2.1** (↑17)	273 13.0±2.5	336 14.0±2.1
Total no. dead fetuses [b] **Dead fetuses/dam [c]**	0 0.0 ± 0.0	0 0.0 ± 0.0	0 0.0 ± 0.0	0 0.0 ± 0.0
Total no. resorptions **Total no. resorptions/dam**	18 0.8±1.2	9 0.4±0.6	16 0.7±0.9	14 0.6±0.9
Early resorptions **Early resorptions/dam**	18 0.8±1.2	7 0.3±0.6	16 0.7±0.9	13 0.5±0.9
Late resorptions **Late resorptions/dam**	0 0.0±0.0	2 0.1±0.3	0 0.0 ± 0.0	1 0.0±0.2
Complete litter resorptions	0	0	0	0
Mean fetal weight (g)	4.8±0.4	4.6±0.4* (↓4)	4.9±0.5	4.9±0.5
Sex ratio (% male)	50.3±13.5	46.9±12.1	52.9±15.3	53.0±13.1
Preimplantation loss (%)	14.5±15.5	6.3±9.7*	11.8±15.7	9.1±11.3
Postimplantation loss (%)	5.6±8.6	2.6±3.9	5.5±6.5	4.1±6.6

a Data were obtained from Tables 4 and 9 on pages 31, 39, and 40 and Appendix 5 on pages 210-213 of the study report.

b The reviewers determined that there were no dead fetuses in each group because the total number of live fetuses in each group + the total number of resorptions were equivalent to the total number of implantations (i.e., all post-implantation loss was accounted for by resorptions and not fetal death).

c Calculated by the reviewers from data presented in this table.

* Significantly different from controls at $p \leq 0.05$

** Significantly different from controls at $p \leq 0.01$

B. DEVELOPMENTAL TOXICITY

1. External examinations: All external malformations are presented in Table 5. There were no treatment-related external findings. All malformations occurred in single fetuses and/or in a manner unrelated to dose.

TABLE 5. External malformations (# of fetuses [# of litters] affected) [a]				
Observation	Dose (mg/kg/day)			
	0	10	30	100
Polydactaly	---	1 (1)	---	---
Cleft palate	---	2 (1)	---	---

a Data were obtained from Table 12 on pages 44-53 of the study report.
--- No animals affected (i.e., zero incidence)

2. **Visceral examinations:** All visceral findings are presented in Table 6. There were no treatment-related visceral findings. All visceral findings occurred with a similar frequency in the treated and control groups and/or in a manner unrelated to dose.

TABLE 6. Visceral findings (# of fetuses [# of litters] affected) [a]					
Observation		Dose (mg/kg/day)			
		0	10	30	100
Ureter	Kinked	19 (8)	36 (12)	13 (4)	28 (12)
	Slightly dilated	2 (2)	5 (4)	2 (2)	2 (2)
Liver	Cyst	---	1 (1)	---	---
	Discolored area(s)	1 (1)	1 (1)	1 (1)	---

a Data were obtained from Table 12 on pages 44-53 of the study report.
--- No animals affected (i.e., zero incidence)

3. **Skeletal examination:** Selected skeletal findings are presented in Table 7. At 100 mg/kg/day, skeletal malformations were limited to 5th and 6th lumbar centra fused in one fetus, and another fetus displaying 13th thoracic arch absent, 13th thoracic hemicentrum partially ossified, and 12th to 2nd lumbar arches misaligned. The proportion of fetuses with minor skeletal defects was similar for all groups, including controls. However, consideration of the specific defects revealed an increased incidence of 100 mg/kg/day fetuses with an unossified 3rd cervical centrum and an increased incidence of litters in the same group with a misaligned 5th sternebra which is regarded as an adverse effect of treatment. The increased incidence of skeletal variants noted in the 10 mg/kg/day group was not considered to be related to treatment because the proportion of fetuses with skeletal variations was similar in the control, 30, and 100 mg/kg/day groups and these findings were observed in a manner unrelated to dose. *Manus* and *pes* scores were comparable in the control, 30 and 100 mg/kg/day groups. The slight increase in *manus* score observed at 10 mg/kg/day was unrelated to dose.

TABLE 7. Skeletal malformations and variations (# of fetuses [# of litters] affected) [a]				
Observation	Dose (mg/kg/day)			
	0	10	30	100
Malformations				
5th and 6th lumbar centra fused	---	---	---	1 (1)
13th thoracic arch absent	---	---	---	1 (1) [b]
13th thoracic hemicentrum partially ossified	1 (1)	---	---	1 (1) [b]
12th thoracic to 2nd lumbar arches misaligned	---	---	---	1 (1) [b]
Variations				
Odontoid – not ossified	59 (16)	116 (23)**	42 (14)	63 (18)
Cervical vertebrae, 2nd – centrum not ossified	85 (21)	119 (23)	68 (20)	97 (21)
Cervical vertebrae, 3rd – centrum not ossified	16 (8)	30 (11)	11 (5)	32* (12)
Cervical vertebrae, 7th –transverse process partially ossified	44 (17)	70 (19)	52 (21)	51 (20)
Sternebrae, 5th – misaligned	---	---	1 (1)	5* (5)
Sternebrae, 5th – partially ossified	67 (20)	110** (22)	64 (18)	79 (21)
Sternebrae, 5th – bipartite	65 (20)	56 (19)	52 (20)	77 (23)
Calcaneum – not ossified	118 (19)	184** (21)	112 (17)	143 (22)
Hindpaws – 6th digit present	---	1 (1)	---	---

a Data were obtained from Table 12 on pages 44-53 of the study report.
b Multiple malformations were observed in the same animal (#92M).
--- No animals affected (i.e., zero incidence)
* Significantly different from controls; $p \leq 0.05$
** Significantly different from controls; $p \leq 0.01$

III. DISCUSSION AND CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: The Investigators concluded that administration of ZA1963 at 100 mg/kg/day resulted in maternal toxicity, as evidenced by decreased body weight gain, decreased food consumption, and increased incidence of animals with diarrhea and urine staining. The maternal NOAEL was 30 mg/kg/day. There was no evidence of an adverse effect on the number, growth, or survival of fetuses *in utero*. There was no evidence of an adverse effect on fetal development. Additionally, consideration of the incidence and type of major and minor defects and variants revealed no treatment-related effects. Therefore, the developmental NOAEL was 100 mg/kg/day.

B. REVIEWER COMMENTS

1. Maternal toxicity: No treatment-related effects on mortality, gross pathology, or cesarean section data were observed in the dams at any dose.

At 100 mg/kg/day, clinical signs including signs of diarrhea, diarrhea, and urine staining were observed in 6-9 animals during the dosing period. Also in this group, body weight gains (calculated by reviewers) were decreased by 22% compared to controls during the dosing period (GD 7-16) and 7% for the overall (GD 1-22) study; body weights were decreased ($p \leq 0.01$) by 3-4% at all intervals during dosing and on GD 19; and food consumption values were decreased ($p \leq 0.01$) by 13-35% compared to controls throughout the dosing period.

The maternal LOAEL was 100 mg/kg/day based on decreased body weight gain, food

consumption, and increased incidence of clinical signs (diarrhea and urine staining). The maternal NOAEL is 30 mg/kg/day.

2. **Developmental toxicity:** There is evidence of treatment-related developmental toxicity, in the form of skeletal variations, observed at the highest dose tested, 100 mg/kg/day.

a. **Deaths/resorptions:** There were no abortions, premature deliveries, complete litter resorptions, or dead fetuses and no effects of treatment on the numbers of litters, live fetuses, or resorptions. Similarly, sex ratio and post-implantation losses of the treated groups were comparable to controls.

b. **Altered growth:** There were no effects of treatment on growth or development of the fetuses. Fetal weights of the treated groups were comparable to controls, and there were no treatment-related effects on ossification of the skeleton.

c. **Developmental variations:** There were no adverse treatment-related external or visceral, variations. At 100 mg/kg/day, an increased incidence of misaligned 5th sternebra was observed and regarded as an adverse effect of treatment.

d. **Malformations:** There were no adverse treatment-related external, visceral, or skeletal malformations.

The developmental LOAEL is 100 mg/kg/day based on misaligned 5th sternebra. The developmental NOAEL is 30 mg/kg/day.

This study is classified **acceptable/guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700a; OECD 414) in rats.

C. **STUDY DEFICIENCIES:** The following minor deficiency was noted but does not affect the acceptability or the conclusions of this DER: historical control data were not provided.

ATTACHMENT

The following is page 61 from the study report.

APPENDIX D - SCALE FOR ASSESSMENT OF SKELETAL OSSIFICATION OF THE *MANUS* AND *PES*

Scale

1 (good) Metacarpals/metatarsals fully ossified. 1st and 3rd rows of phalanges fully ossified.

2 Metacarpals/metatarsals fully ossified. 1st and 3rd rows of phalanges fully ossified, although an occasional phalanx (no more than 2) may be partially ossified.

3. Metacarpals/metatarsals fully ossified. Several phalanges from 1st and 3rd rows may be partially or not ossified with the remainder being fully ossified.

4. Some metacarpals/metatarsals partially ossified, the remainder being fully ossified. Several phalanges (no more than 6) from 1st and 3rd rows may be partially or not ossified.

5. Some metacarpals/metatarsals partially ossified, the remainder being fully ossified. The majority of phalanges from 1st and 3rd rows (i.e. more than 6) will be partially or not ossified, the occasional phalanx may be fully ossified.

6. (poor) Some metacarpals/metatarsals partially or not ossified the remainder being fully ossified. 1st row of phalanges usually not ossified and the 3rd row of phalanges partially or not ossified.